Levodopa in Parkinsonism : reduction in the electromyographic silent period and its relationship with tremor

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SUMMARY The electromyographic silent period after electrical stimulation of the median nerve was recorded by surface electrodes over the abductor pollicis brevis muscle in 32 patients with Parkinsonism before and after treatment with levodopa. A supra-maximal stimulus was delivered during maximal isometric contraction of the muscle. The silent period was prolonged in the untreated state compared with controls, but shortened significantly as a result of treatment. Observation of the clinical effects of treatment in each patient showed a relationship between shortening of the silent period and improvement in resting tremor. There was no relationship between the duration of the silent period and rigidity. The significance of these findings is discussed. They are considered to support the view that inhibition of motoneurone activity by afferent stimuli is intensified in Parkinsonism and that there is a close relationship between the degree of motoneurone inhibition and the severity of tremor.

The electromyographic silent period (Merton, 1951) after electrical stimulation of a motor nerve was reported to be prolonged in patients with Parkinsonism by Pinelli (1955) and later by Hufschmidt (1959) who found values of 120 to 180 msec in the biceps muscle in eight patients compared with 80 to 100 msec in controls. Hufschmidt considered that the silent period was a consequence of Golgi afferent inhibition of motor neurones and that the prolonged silent period in Parkinsonism resulted from increased excitation (or diminished inhibition) of spinal interneurons relaying these impulses to motor neurones. He demonstrated that the timing of the tremor could be 're-set' by sudden repositioning of the limb or by electrical stimulation of the peripheral nerve and argued that the tremor could be explained entirely on the basis of recurrent synchronization of motor neurones activity alternating with autogenous muscular inhibition. Using a slightly different technique Hofmann (1962a, b) studied eight patients with Parkinsonism and found that the silent period was reduced in those whose main disability was rigidity. In those with tremor he reported that the silent period was normal between tremor bursts but completely absent during tremor

bursts. He concluded that fusimotor activity was decreased in Parkinsonism which accentuated tremor by removing length-servo feedback, the tension-servo system being intact. Angel, Hofmann, and Eppler (1966) attempted to isolate the effects of fusimotor activity by suddenly unloading muscles rather than by stimulating them electrically; using this technique they showed no difference between five treated patients with Parkinsonism and control subjects. Patients with rigidity but without significant tremor were reported to have normal silent periods by Dietrichson (1971).

These apparently contradictory reports are surprising, especially as their authors all agree with Merton (1951) that the silent period is a consistent and reproducible phenomenon. In their survey of the silent period in normal subjects Higgins and Lieberman (1968a) showed that the 'normal' range varied from one series to another and was not as sharply demarcated as previously supposed. They suggested that differences in technique could be responsible and that adequate controls were therefore essential in any study of the silent period. The effectiveness of levodopa in reversing some of the clinical abnormalities of Parkinsonism has provided

an opportunity of measuring silent periods in the same patients before and after clinical response to the drug.

METHODS

The patients studied were suffering from idiopathic, postencephalitic or arteriosclerotic Parkinsonism. Most had been referred to the unit because of an unsatisfactory response to anticholinergic drugs and some were severely disabled. None had previously received levodopa. There were 17 males and 15 females, the ages varying from 36 to 74 years (mean age 55 years). All had rigidity of some degree in both upper limbs, except one patient whose rigidity and tremor were confined to the right upper and lower limbs. Twelve patients had unilateral tremor and of these 11 had bilateral rigidity; the rigidity tended to be more pronounced on the side affected by tremor. Seventeen patients had bilateral tremor and three had no tremor (Table 1).

TABLE 1
PATIENTS STUDIED

	<i>Patients (no.)</i>
Bilateral rigidity and bilateral tremor	17
Bilateral rigidity with unilateral tremor	11
Bilateral rigidity with no tremor	3
Unilateral rigidity with ipsilateral tremor	1
Total	32

Fifteen patients from neurological wards, none of whom had evidence of extrapyramidal system disorder, were used as controls. Their ages ranged from 39 to 72 years (mean age 57 years).

The silent periods on right and left sides were measured (1) at least 48 hours after withdrawal of all anti-Parkinsonism drugs, and (2) at least 48 hours after maximum dosage (the maximum dose that caused no side-effects) had been reached. The dose attained varied from 2.0 to 8.0 g daily. No other drugs were prescribed apart from night sedation and, in two patients, diazepam. Clinical assessments of tremor amplitude and of rigidity were made before, during, and after treatment, and the patient was also asked for his own assessment of tremor because of the variability of this symptom. Nine patients agreed to withdraw levodopa completely and their silent periods and clinical state were reassessed after they had had no treatment for at least four days.

The silent period was measured bilaterally by the same technique in all 32 patients and in the 15 controls. After preparation of the skin with standard electrode jelly, skin-clip surface electrodes were

FIG. 1. The effect of a supramaximal stimulus upon EMG activity during maximal voluntary contraction. The silent period is the interval between the stimulus S and the onset of uninterrupted voluntary activity X. F is the F wave of Magladery and Mac Dougal (1950).

FIG. 2. The same patient as Fig. 1. If a weaker stimulus is used, a burst of voluntary activity breaks into the silent period during maximal contraction. The S-X interval may be correspondingly prolonged.

placed 3 cm apart over the belly of the abductor pollicis brevis muscle. Stimulating electrodes 3 cm apart with the cathode distal to the anode were placed over the median nerve at the lower end of the forearm. After confirming that the stimulating electrodes were correctly positioned to provide a supramaximal stimulus the patient was asked to maintain a maximal voluntary contraction isometrically against his clenched fist. A constant-voltage supramaximal stimulus was delivered from a DISA Ministim stimulator, which simultaneously triggered a storage oscilloscope (Tektronix RM 564). The voltage difference between the recording electrodes was fed

through a Medelec pre-amplifier to an EMG main amplifier (total gain $\times 40,000$) and displayed on the oscilloscope.

The silent period was taken as the interval between the electrical stimulus and the onset of uninterrupted voluntary contraction (Fig. 1). This has been called the S-X interval by Higgins and Lieberman (1968a) and may include the direct response of the muscle to stimulation of motor nerve fibres, the F wave (Magladery and MacDougal, 1950), and in certain circumstances a burst of 'voluntary activity' (Merton, 1951). This latter activity (Fig. 2) is seen at high isometric tensions and low stimulus intensities, and if it is allowed to appear the end of the silent period may be correspondingly delayed (Merton, 1951). The strength of the electrical stimulus was therefore increased beyond the level necessary for a maximal direct response until no 'voluntary activity' was seen between the F wave and the end of the silent period (Fig. 1). This was normally achieved with a square-wave stimulus of 500 V lasting 0.1 msec. The stimulus was not increased beyond 0.2 msec at 500 V in order to avoid excessive discomfort for the subject. There was no difficulty in obtaining a consistent result provided that voluntary contraction was maintained at its maximum and a stimulus of sufficient intensity was employed. If these conditions were met, the phase of tremor at the moment of stimulation did not affect the silent period. The stimuli were given at random intervals until at least six consecutive identical values were obtained. The results were analysed statistically by the paired *t* test.

RESULTS

The mean silent period of the 32 patients before treatment was 124.9 msec, compared with the mean of 96.1 msec for the controls. The patients with bilateral tremor had even longer silent

periods (mean 134.2 msec), while those with unilateral tremor had longer silent periods in the affected hand than in the unaffected hand (Table 2). The longest silent period in an untreated patient was 200 msec (severe bilateral tremor and rigidity) and the shortest was 80 msec (severe bilateral rigidity but no tremor). The longest silent period recorded in a control subject was 125 msec and the shortest was 80 msec.

Clinically the patients' response to treatment with levodopa was favourable. Rigidity improved in every case. Tremor improved in 25 of the 32 cases, being abolished in nine; three patients showed no change and one became worse. The remaining three patients had shown no resting tremor when untreated. In nine patients levodopa was subsequently withdrawn and all deteriorated considerably.

There was a significant shortening of the mean silent period for all 32 patients after treatment with levodopa (Table 2), from 124.9 msec to 109.4 msec ($P < 0.01$). Twelve patients had unilateral tremor and 11 of these had bilateral rigidity: after levodopa there was a significant shortening of the silent period in the hands affected by tremor ($P < 0.01$) but not in the contralateral hands, despite improvement in rigidity on both sides. The shortening of the silent period in patients with bilateral tremor was even more pronounced and both groups after treatment had a mean silent period of about 109 msec.

In 14 hands, tremor was abolished by levodopa; after treatment the longest silent period in these hands was 105 msec and the mean was 94.5 msec, which is not significantly different from the mean control value of 96.1 msec.

Although rigidity tended to be more pronounced in limbs that were subject to severe tremor, changes in the silent periods of individual patients during treatment could not be correlated with rigidity alone. The three patients with marked bilateral rigidity but no tremor showed no shortening of the silent period during treatment, despite a considerable improvement in rigidity. The patient with unilateral rigidity and tremor showed lengthening of the silent period in the affected hand (115 to 135 msec) during treatment; this increase was accompanied by worsening of the tremor but slight improvement in rigidity. Only two other patients showed lengthening of the silent period during levodopa treatment; neither had tremor before treatment but their rigidity was improved by treatment.

TABLE 2
SILENT PERIODS—MEAN VALUES AND STANDARD DEVIATION (SD)

<i>Patients</i>	<i>Untreated (msec)</i>	<i>During treatment (msec)</i>	<i>Probability P</i>
All 32 patients with Parkinsonism	124.9 (SD 21.8)	109.4 (SD 17.3)	< 0.01
12 Patients with unilateral tremor: affected hand	122.3 (SD 21.2)	109.2 (SD 13.7)	< 0.01
unaffected hand	111.3 (SD 16.5)	110.4 (SD 13.0)	Not significant
17 Patients with bilateral tremor	134.2 (SD 21.8)	106.2 (SD 20.1)	< 0.01

Nine patients discontinued levodopa after the second assessment. Before treatment the mean silent period for these nine patients was 118.4 msec; it fell during treatment to 112.6 msec, and rose to 123.8 msec after withdrawal of the drug ($P < 0.02$). This indicates that the effect of levodopa on the silent period, like its clinical effect, is reversed when the drug is withdrawn.

Shortening of the silent period during treatment did not depend upon the presence of a high initial value: one of the patients with rigidity but no tremor had a silent period of 130 msec which did not change during treatment. Conversely, a patient with little rigidity but marked tremor showed a decrease in the silent period from 110 to 90 msec accompanied by improvement in her symptoms.

DISCUSSION

These results indicate a relationship between the silent period of voluntarily innervated muscle, produced by indirect electrical stimulation, and the tremor of Parkinsonism. Prolongation of the silent period is not a feature of all cases of Parkinsonism; previous reports of prolonged silent periods in Parkinsonism have in fact been based on patients in whom tremor was pronounced (Pinelli, 1955, Hufschmidt, 1959), while normal silent periods have been found in patients without significant tremor (Angel *et al.*, 1966; Dietrichson, 1971). The contrary results of Hofmann (1962a, b) can be explained by the fact that he used a much weaker stimulus superimposed on a gentle voluntary contraction, considering that 'the slightest visible twitch of the thumb adductor was all that was required'. Under these conditions the second phase of the silent period may be extinguished and the silent period appears to be short (Fig. 3).

Although Merton (1951) did not consider that a supramaximal stimulus was necessary, his tracings show prolongation of the silent period by about 20 msec when stimuli were increased beyond threshold levels. The use of a supramaximal stimulus is particularly important in conditions of high tension of contraction. Under such conditions voluntary activity may break into the silent period at about 60 msec (Fig. 2), delaying the end point (Merton, 1951). Herman (1969) was unable to obtain a silent period in the soleus or gastrocnemius muscles during maximal isometric contraction even with a supramaximal stimulus. Both these authors presented convinc-

FIG. 3. The effect of increasing stimulus intensities during gentle isotonic contraction in Parkinsonism. A, barely suprathreshold stimulus of 300 V. B, stimulus of 350 V. C, stimulus of 500 V. The apparently short S-X interval in A is an artefact produced by breakthrough voluntary activity V.

ing evidence that antidromic stimulation of motoneurons does not affect the end point of the silent period.

On the basis of observations in five normal subjects Higgins and Lieberman (1968b) suggested that the effects of inhibition by Golgi tendon organs were confined to the early part of the silent period, before the burst of break-

through voluntary activity. They did not superimpose supramaximal stimuli on maximal isometric contraction and their technique was designed to minimize activation of Golgi tendon organs by the twitch contraction. Their conclusions were drawn partly from measurements of the period of electrical silence between breakthrough voluntary activity and the end point of the silent period (V-X interval, Fig. 2). Although designated by them as the 'F-X interval', this period of silence was not the interval between the F wave and the end of the silent period, which would be a better definition of the term. The duration of the period of electrical silence that was actually measured is affected mainly by changes in the duration of breakthrough voluntary activity; it is not accompanied by corresponding changes in the timing of the end point of the silent period measured from the stimulus (S-X interval). Herman (1969) concluded from studies of the soleus and gastrocnemius muscles that the duration of the silent period was controlled by a pause in the discharge from primary endings in the muscle spindles. While this may be true for conditions of gentle voluntary contraction and passive stretch, during voluntary isometric contraction at high tensions the magnitude of the added twitch tension was directly related to an increase in the duration of the silent period. In these particular circumstances prolongation of the silent period by afferent impulses from Golgi tendon organs has not been excluded. It is possible that spindle bias, Golgi, and other inhibitory activities can affect the duration of the silent period, but that the precise balance of these components varies according to the technique employed.

The term 'spindle bias' needs qualification. Primary and secondary afferent receptors are activated by different mechanical stimuli and their sensitivity is separately controlled; furthermore, the direction of their reflex effects on alpha motoneurone activity not only differs but may be modified or reversed by supraspinal influences (Matthews, 1971). From his analysis of the stretch reflex in the decerebrate cat, Matthews (1970) postulated a scheme in which afferent impulses from secondary spindle receptors increased motoneurone excitability not by direct facilitation but by inhibiting impulses from Golgi tension receptors. Reduction in tonic fusimotor activity could in this way increase the inhibitory effect of impulses from Golgi tension receptors, as well as delaying the

activation of facilitatory spindle receptors during the re-extension that follows a twitch contraction.

In their studies of the tremor of Parkinsonism, Hufschmidt (1959) and Hofmann (1962a) empha-

FIG. 4. Synchronization of tremor bursts in the *abductor pollicis brevis* muscle after supramaximal stimulation of the median nerve. The oscilloscope was triggered by stimuli at random time intervals; 25 traces superimposed.

sized the importance of peripheral factors in the timing and amplitude of tremor. In particular the observation that tremor-bursts can be re-set by stimulating the peripheral nerve was confirmed on several occasions during the course of the present study (Fig. 4), though not in patients receiving treatment. Generous supramaximal stimulation is likely to have activated all types of efferent and afferent fibre running in the nerve. Whatever the precise mechanism, a relationship has been established between the inhibitory effect of peripheral stimulation in Parkinsonism and the amplitude of tremor. Moreover, the beneficial effect of levodopa on the tremor of Parkinsonism is very closely linked with a lessening of the inhibiting effect of peripheral stimuli on the motoneurone. Only three patients responded atypically to levodopa by an increase of motoneurone inhibition: one experienced an increase in the amplitude of tremor while the other two had no tremor during the period of investigation. Bergmans and Grillner (1968) and Grillner (1969) have shown that the administration of levodopa to animal preparations increases activity in static fusimotor neurones but decreases the discharge of dynamic fusimotor

neurones. The hypothesis of Matthews (1970) to which reference has already been made would explain how such a mechanism might contribute to the relief of tremor. In Parkinsonism, levodopa does not shorten the silent period in limbs that are not subject to tremor. This suggests that levodopa does not have a general effect on segmental neurones but is specifically reversing a pathological disturbance of motoneurone control.

Levodopa reduced the rigidity of Parkinsonism but this reduction, unlike the reduction in tremor, did not correlate with shortening of the silent period. Using a different technique, Higgins, Haidri, and Wilbourn (1971) also found no change in the silent period when rigidity and bradykinesia were improved by levodopa. Local anaesthetic injected into the belly of a rigid muscle (Walshe, 1924; Rushworth, 1960) reduces the rigidity; although the rate and rhythm of tremor are altered its amplitude may actually increase (Hofmann, 1962a). The reduction in rigidity has been interpreted variously as indicating that rigidity is produced by tonic activity of gamma motoneurones (Rushworth, 1960), by reduced reciprocal inhibition due to underactivity of gamma motoneurones (Hofmann, 1962a), or by potentiation at spinal cord level of facilitatory impulses from Ia afferent fibres (Ward, 1968). The electromyographic abnormalities in Parkinsonism were reviewed by Simpson (1966), who presented evidence for increase of both facilitation and inhibition of motoneurones, and argued that the resting tremor of Parkinsonism was due to an interaction of increased activity in supraspinal facilitatory and inhibitory systems. This hypothesis implies that a reduction in the excessive activity of either system would diminish tremor. Preferential reduction of inhibitory activity would be expected to diminish tremor without affecting rigidity. The present findings show that although in some patients treatment with levodopa reduces rigidity without improving tremor, improvement in tremor is accompanied by a reduction of the inhibitory effect of peripheral stimuli. This suggests that motoneurone inhibition is more important than facilitation in the genesis of tremor.

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